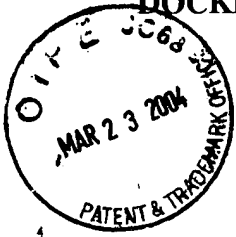


DOCKET NO.:ALZA-0020

PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lam, et al.

Confirmation No.: 5468

Application No.: 09/253,317

Group Art Unit: 1614

Filing Date: February 19, 1999

Examiner: Zohreh A. Fay

For: Methods and Devices for Providing Prolonged Drug Therapy

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPLEMENTAL DECLARATION OF SUNEEL K. GUPTA

I, Suneel K. Gupta, hereby declare that:

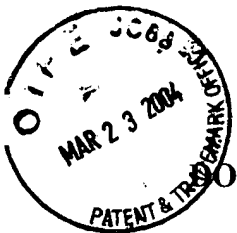
1. I am the same Suneel K. Gupta who already submitted a declaration in connection with the above-identified patent application.

2. I have been asked to assess the extent to which one can determine the rate at which the Ritalin SR product releases methylphenidate based on the plasma concentration data for that product that are provided in Hubbard, *et al.*, *Journal of Pharmaceutical Sciences* **1989**, 78:11, 944 ("the Hubbard reference"). To make this determination, I supervised application of the Wagner-Nelson mathematical deconvolution method (Wagner, *et al.*, *Journal of Pharmaceutical Sciences* **1963**, 52, 610) to the plasma concentrations that the Hubbard reference discloses in Figure 1 for "Patient Profile 2" and in Figure 2. This type of deconvolution is routinely performed by those skilled in the field of drug delivery, and I have deconvoluted

plasma concentration data or supervised the deconvolution of such data numerous times during the course of my career.

3. - By deconvoluting the above-noted plasma concentration data that the Hubbard reference discloses, one is able to approximate the release rate that the Ritalin SR product would have needed to achieve to produce the plasma concentrations that the reference reports. Although there exist a number of different methods that potentially could be used to deconvolute the Ritalin SR plasma concentration data that the Hubbard reference provides, the Wagner-Nelson method was one of the first to appear in the literature and one that I believe to produce representative results.

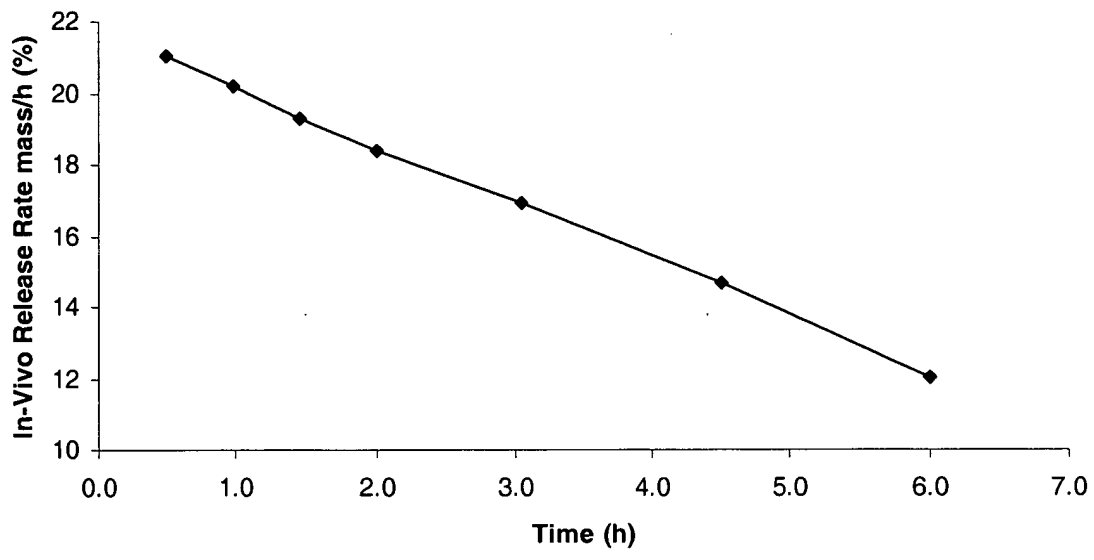
4. By applying the Wagner-Nelson method to the above-noted data that the Hubbard reference reports, I was able to determine that the methylphenidate release rate for the Ritalin SR actually decreased during the 6-hour period over which the authors gathered their data. This is shown in the following graphs plotting the data that I obtained using the Wagner-Nelson method. Note that to simplify the analysis, these graphs reflect the combined release rates for the methylphenidate enantiomers that the figures in the Hubbard reference characterize separately with respect to their respective plasma concentration. This combination, however, does not alter the general trend of decreasing release rate that one observes.



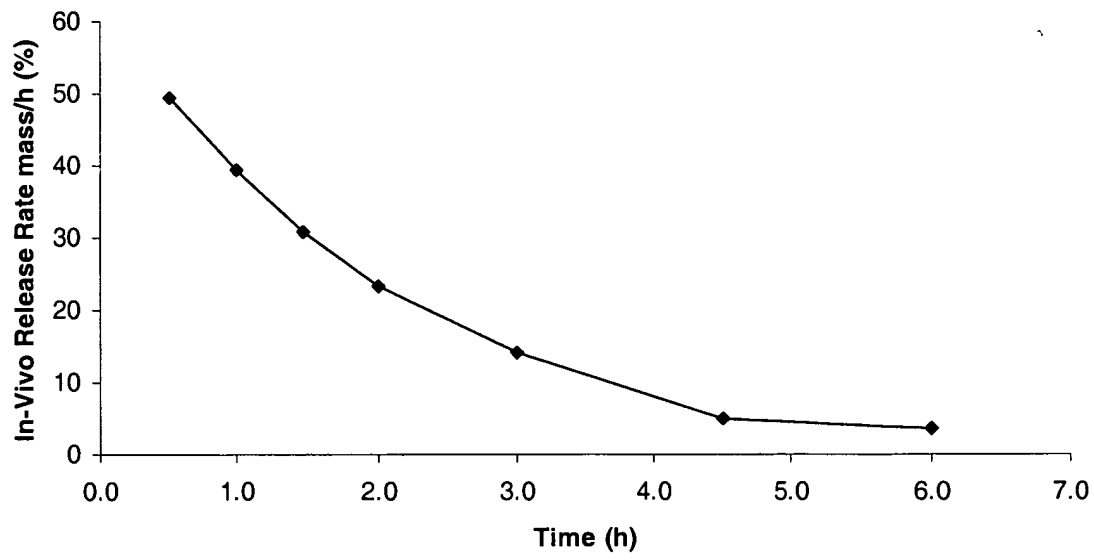
BUCKET NO.:ALZA-0020

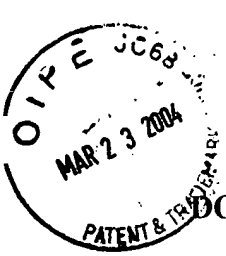
PATENT

**Release Rate Profiles For Patient 2
Following Methylphenidate Treatment
Calculated Using Wagner-Nelson Method for Ritalin SR**



**Release Rate Profile For Mean Data
Following Methylphenidate Treatment
Calculated Using Wagner-Nelson Method for Ritalin-SR**





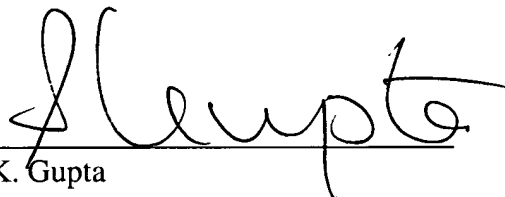
DOCKET NO.:ALZA-0020

PATENT

I do not believe that anyone skilled in the field of drug delivery would consider this to constitute the “ascending release rate over an extended period of time” that I understand to be recited in the claims of the above-identified patent application.

5. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

March ^{19th} __, 2004


Suneel K. Gupta